

RESEARCH MONOGRAPH . COMPOUND PROFILE

Orforglipron

A small-molecule oral GLP-1 receptor agonist developed by Eli Lilly that does not require absorption of an intact peptide, distinguishing it from the peptide-class oral semaglutide formulation.

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ABSTRACT

Orforglipron (LY3502970; CAS 2212020-52-3; molecular formula C₄₂H₅₅F₃N₆O₅; molecular weight 781.07) is a small-molecule non-peptide GLP-1 receptor agonist developed by Eli Lilly through licensing of a chemical series originated by Chugai

Pharmaceutical and further optimized at Lilly. The compound is the first true small-molecule oral GLP-1 agonist to enter Phase 3 clinical trials; the only previously marketed oral GLP-1 agonist is the peptide-class oral semaglutide (Rybelsus), which requires the SNAC absorption-enhancer formulation and a strict fasted-state administration protocol owing to the intrinsically poor oral bioavailability of peptide GLP-1 agonists. The non-peptide structure of orforglipron eliminates the absorption challenge: oral bioavailability is approximately 30 to 60 percent without absorption enhancers and without strict fasting requirements; the compound is an allosteric agonist that binds at a site distinct from the GLP-1 peptide binding pocket, producing receptor activation through a non-peptide chemical scaffold. Phase 2 obesity results published in 2023 reported approximately 14.7 percent body weight reduction at 36 weeks at the highest dose, comparable to subcutaneous semaglutide and meaningfully greater than oral semaglutide at clinically used doses. Phase 2 type 2 diabetes results showed glycated hemoglobin reduction up to 2.1 percent at the highest dose. The compound is in active Phase 3 development in obesity (ATTAIN program) and type 2 diabetes (ACHIEVE program) with anticipated regulatory submissions in 2025 to 2026. Side effect profile parallels other GLP-1 agonists (nausea, vomiting, diarrhea) with somewhat more rapid onset of adverse events at initiation, attributed to the rapid absorption profile of

the small molecule versus the slow titration enabled by long-acting injectable peptides. Orforglipron represents a category-shifting development in the GLP-1 class: oral, simple administration, and competitive efficacy.

1. Compound Identification

Orforglipron is described as oral non-peptide glp-1 receptor agonist (small molecule). A small-molecule oral GLP-1 receptor agonist developed by Eli Lilly that does not require absorption of an intact peptide, distinguishing it from the peptide-class oral semaglutide formulation.

1.1 Class summary

Oral non-peptide GLP-1 receptor agonist (small molecule)

1.2 Subtitle

A small-molecule oral GLP-1 receptor agonist developed by Eli Lilly that does not require absorption of an intact peptide, distinguishing it from the peptide-class oral semaglutide formulation.

2. Abstract

Orforglipron (LY3502970; CAS 2212020-52-3; molecular formula C₄₂H₅₅F₃N₆O₅; molecular weight 781.07) is a small-molecule non-peptide GLP-1 receptor agonist developed by Eli Lilly through licensing of a chemical series originated by Chugai Pharmaceutical and further optimized at Lilly. The compound is the first true small-molecule oral GLP-1 agonist to enter Phase 3 clinical trials; the only previously marketed oral GLP-1 agonist is the peptide-class oral semaglutide (Rybelsus), which requires the SNAC absorption-enhancer formulation and a strict fasted-state administration protocol owing to the intrinsically poor oral bioavailability of peptide GLP-1 agonists. The non-peptide structure of orforglipron eliminates the absorption challenge: oral bioavailability is approximately 30 to 60 percent without absorption enhancers and without strict fasting requirements; the compound is an allosteric agonist that binds at a site distinct from the GLP-1 peptide binding pocket, producing receptor activation through a non-peptide chemical scaffold. Phase 2 obesity results published in 2023 reported approximately 14.7 percent body weight reduction at 36 weeks at the highest dose, comparable to subcutaneous semaglutide and meaningfully greater than oral semaglutide at clinically used doses. Phase 2 type 2 diabetes results showed glycated hemoglobin reduction up to 2.1 percent at the highest dose. The compound is in active Phase 3 development in obesity (ATTAIN program) and type 2 diabetes (ACHIEVE program) with anticipated regulatory submissions in 2025 to 2026. Side effect profile parallels other GLP-1 agonists (nausea, vomiting, diarrhea) with somewhat more rapid onset of adverse events at initiation, attributed to the rapid absorption profile of the small molecule versus the slow titration enabled by long-acting injectable peptides. Orforglipron represents a category-shifting development in the GLP-1 class: oral, simple administration, and competitive efficacy.

3. Mechanism of Action

Allosteric small-molecule agonism at the GLP-1 receptor at a site distinct from the peptide binding pocket. Receptor activation produces appetite reduction, slowed gastric emptying, and glucose-dependent insulin secretion equivalent to peptide GLP-1 agonists.

The mechanistic profile described above represents the consensus position from peer-reviewed literature where available; for compounds with sparse formal characterization, this section reflects vendor-grade reports and structurally-related class pharmacology and should be interpreted with appropriate caution.

4. Pharmacokinetics and Routes of Administration

Pharmacokinetic data are summarized within the abstract for compounds with formal Phase 1 records. Compounds without published human pharmacokinetic studies are noted as such; investigators should treat the absence of data as a research limitation.

5. Reported Research Dose Ranges

Phase 2 obesity 12 to 45 mg per oral administration once daily. Phase 3 dosing across this range with titration.

Doses are scaled from clinical use where the compound is approved as a medicine, from Phase 2/3 trials where development advanced, or from rodent dose-response data scaled by allometric assumptions where the compound has no human clinical record. Investigators should treat dose ranges from research-chemical-grade vendors as starting points for their own pharmacokinetic and tolerability characterization rather than validated dosing recommendations.

6. Sourcing and Quality Verification

Investigators should obtain analytical confirmation of identity (mass spectrometry; for peptides, additionally amino acid analysis or N-terminal sequencing) and purity (HPLC area-percent, ideally greater than 95 percent) on every lot. Vendor certificates of analysis vary in quality; third-party analytical confirmation through independent laboratories (e.g., Janoshik Analytical, Anabolic Lab) is the gold standard for research-grade peptides and small molecules.

For compounds with established pharmaceutical-grade marketing in any jurisdiction, sourcing from the marketed product (where legal and accessible) provides the highest quality assurance.

7. Reconstitution and Handling

Peptides should be reconstituted in bacteriostatic water or sterile water for injection in the volume appropriate to the desired concentration; lyophilized peptides should be allowed to come to room temperature before reconstitution to minimize precipitation. Reconstituted peptides should be stored refrigerated and used within the timeframe specified by the manufacturer (typically 14 to 30 days for bacteriostatic water reconstitutions, shorter for sterile water).

Small molecules: storage conditions vary by compound; consult the certificate of analysis for the specific product. Most are stable at room temperature in dry, dark conditions; oxidation-sensitive compounds (e.g., catecholamine precursors) require cool storage and protection from light.

8. Stack Interaction Considerations

Investigators combining this compound with other research substances should consider receptor-level interactions (additive effects at shared targets), enzyme-level interactions (CYP-mediated drug-drug interactions where applicable), and pharmacodynamic interactions (additive sedation, additive serotonergic activity, additive hemodynamic effects).

The stack interaction section in published monographs of well-characterized compounds is necessarily incomplete for any specific combination; investigators should treat novel combinations with elevated caution and titrate gradually.

9. References

1. Wharton S, et al. Daily oral orforglipron in obesity. N Engl J Med 2023.
2. Frias JP, et al. Efficacy and safety of orforglipron in type 2 diabetes. Lancet 2023.
3. Eli Lilly. ATTAIN and ACHIEVE Phase 3 programs. R&D update 2024.

This monograph is provided for research use only. Not for medical, diagnostic, or therapeutic purposes. Not for human consumption. Compound class generalizations are noted where compound-specific data are sparse; investigators should weight the evidence accordingly.